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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/964,042	09/26/2001	Ralph Weichselbaum	27373/36638A	1056

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EXAMINER	
PURI, BEENA	
ART UNIT	PAPER NUMBER
1633	3

DATE MAILED: 01/15/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/964,042	WEICHSELBAUM ET AL.	
	Examiner	Art Unit	
	Beena Puri	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspond nc address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____ .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 1-9 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 1-9 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

1. This application is continuation of U.S. application serial No. 09/629,021, filed on July 31, 2000.

2. ***Oath/Declaration***

The oath or declaration is defective. A new oath or declaration in compliance with 37 CFR 1.67(a) identifying this application by application number and filing date is required. See MPEP §§ 602.01 and 602.02.

The oath or declaration is defective because the photocopying of the original Oath has deleted portions of the oath. Parts of the oath are unreadable.

3. ***Claim Rejections - 35 USC § 112***

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim(s) 1-9 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The following factors have been determined by the courts to be critical in determining whether a claimed invention is enabled (See In re Wands 8 USPQ 2d 1400, Fed. Cir. 1988).

The nature of the invention: The instant claims are drawn to a method for killing cancer cells in an individual comprising administering an amount of recombinant Herpes simplex virus (HSV) wherein said HSV genome is modified: by insertion of one or more nucleotides and/ or by deletion of all or part of the coding region or regulatory region of the $_{\gamma 1}$34.5 gene such that one $_{\gamma 1}$34.5 gene remains intact and where in said amount of HSV is being effective to kill cancer cells. Claims are further drawn to a method for killing cancer cells in central and non-central nervous system cancers. Thus, the nature of the invention is a therapeutic use of attenuated HSV virus for cancer and falls in the realm of gene therapy, particularly targeting.

The state of the prior art and the predictability or unpredictability of the art: At the time of filing, the relevant art considered gene therapy as a whole to be extremely unpredictable. Efficacious, predictable modes of delivery that would provide efficient delivery and expression of genes encoding the protein in the target cells had not been developed. **Verma et al.,** (1997) states that gene delivery is the "Achilles heel" of gene therapy, and that the ability to deliver and expression genes efficiently to obtain sustained expression is needed for effective therapy and further notes that although "The use of viruses is powerful technique, because many of them have evolved a specific machinery to deliver DNA to cells. However, humans have an immune system to fight off the virus, and our attempts to deliver genes in viral vectors

have been confronted by these host responses" (pg. 293, col. 3, parag. 1). **Chamber** et al., (1995) previously attributed the greater survival benefit for glioma-bearing mice treated with a $_{\gamma 1}$34.5 mutant in which the 34.5 gene is interrupted by a stop codon (R4009) rather than by deletion (R3616) due to the low level of stop codon suppression in R4009 allowing for enough viral replication so as to effectively destroy tumor cells, yet not multiply to a level where it can cause encephalitis and taught that the "key to the development of effective oncolytic viruses may well depend on precise control of the expression of the $_{\gamma 1}$34.5 gene" and that "this observation may be exploited to construct still more effective viruses" (page 1415, left column). **Advani** (1998) teaches that "While attenuated herpesviruses alone have not been tested in humans, the available date in experimental animals do not predict a high cure rate (page 162, left column) and that "infection alone produced few cures and the majority of infected tumors either grew more slowly or outpaced cell destruction" (page 162, top right column). **Crystal** (1995) has previously recited that "human are not simply large mice. There have been several surprise examples, in which predictions from gene transfer studies in experimental animals have not been borne out in human safety and efficacy trials" (page 409, bottom, left column). Without an art recognized nexus between the results obtained in animal models and the results which the skilled artisan would reasonably expect to see in humans, the results of applicants animal model data are difficult or impossible to interpret.

The above references acknowledge the usefulness of gene therapy for the treatment of cancer and other diseases in the future, however, they also illustrate that there are numerous obstacles that the specification would need to overcome.

The breadth of the claims and the amount of direction or guidance presented in the specification and the presence or absence of working examples:

As such, the disclosed claims are very broad and read on killing any cancer cells by delivering HSV by any route to an individual. Clearly, systemic administration of an attenuated oncolytic herpesvirus by intramuscular injection will have little or no efficacy against a glioblastoma, wherein the blood brain barrier restricts entry into the brain of 120 nm HSV particles (Muldoon et al., 1995). Also, the specification does not provide sufficient guidance on which mutants to use beyond HSV $_{\gamma 1}$34.5 mutants or which HSV $_{\gamma 1}$34.5 mutants exhibit the requisite level of $_{\gamma 1}$34.5 expression in accordance with the teachings and considerations disclosed by Chambers et al., (1995). That is the statement concerning lack of reference between the in vivo nude mouse model data presented by applicants and results which skilled artisan would expect in humans. Without guidance from the specification or the prior art, empirical experimentation would be required to determine an effective amount to treat glioblastoma, prostate adenocarcinoma and hepatoma in the individual.

The quantity of experimentation: To attempt to practice the claimed invention in humans, one of skill in the art would turn to the specification for guidance in practicing the invention. As set forth above, however, the specification lacks sufficient guidance to surmount the technical difficulties recognized in the art. Another source of guidance for

one skilled in the art, the prior art, again for reasons set forth above, also lacks solutions to overcome the considerable list of obstacles recognized in the field. In the absence of working examples from the specification and the prior art, one of skilled in the art would resort to trial and error experimentation to navigate the obstacles to practicing the claimed invention. Again, as established above, solutions to these technical problems have been elusive despite an enormous amount of experimentation due to a number of factors, including the unpredictable nature of the art. Such unpredictability would warrant even more experimentation, with no true expectation of a measure of success. The amount of experimentation required to practice the claimed invention embodiments would necessitate undue experimentation on the part of one skilled in the art.

In conclusion, given the nature of the invention, the state of the art, the lack of predictability found in the art, the breadth of the claims, the amount of guidance set forth in the specification, and the working example set forth it is concluded that the amount of experimentation necessary to practice the invention is very high and is in fact undue.

The following art rejections are based upon the broadest interpretation of the claims. Since it is unclear if the claims are limited to treatment of humans for cancer, the claims are read as including treatment of any individual organism (i.e. mice) for cancer.

4. ***Claim Rejections - 35 USC § 102***

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-9 are rejected under 35 U.S.C. 102(b) as anticipated by Martuzza et al., (U.S. 5,585, 096).

Martuzza recites a method for killing malignant brain tumor cells in vivo (See abstract, column 2). They further teach administration of HSV mutants with additional alterations (ribonucleotide reductase gene) in the unique long region (U_1) of the HSV genome for in vivo tumor cell killing. They teach the construction of said mutant (Example 1, column 13-15) and administration of mutant virus for intracerebral brain tumor killing (Example 4, column 20-21). Furthermore, Martuzza discloses embodiments for treatment of noncentral nervous system cancers (Example 2, column 18, lines 6-8).

Thus, the instant claims are rejected.

5. Claims 1-5, 7, and 9 are rejected under 35 U.S.C. 102(b) as being clearly anticipated by Advani et al. (1997) or (1998).

Advani et al (1997 & 1998) teaches the methods of treating a nervous system cancer, glioblastoma, in athymic mice comprising a human glioma xenograft with attenuated herpes simplex viruses comprising deletion of one- (R7020) or two (R3616) copies of the γ_1 34.5 gene. Advani (1997) recites a figure that appears to be an identical figure 3 disclosed by Advani (1998). In both publications, Advani teaches that attenuation compromises virus replication and potential efficacy and teaches, explicity or implicity, that R7020 is less attenuated and more efficacious for tumor compared with

R3616. The R7020 virus further comprises an additional alteration in a unique region. Therefore, Advani et al., (both references) teach the claimed invention.

6. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim(s) 1-9 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 recites "an individual" that makes the claim indefinite because it does not indicate clearly what it is directed to, or what its metes and bound are, i.e. is an individual limited to humans?. Claims 2-9, being dependent on claim 1, are rejected.

Claim 5 recites an alteration in a "unique region" of HSV genome. Since it is not clearly defined whether this term refers to a particular art-recognized designation or whether it embraces any region that is unique to an HSV genome (as compared to e.g., a Marck's diseases herpesvirus genome, or another herpesvirus- or even non-herpes genome).

7. No claims are allowed.

8. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Beena Puri, Ph. D. whose telephone number is (703)-306-0284. The examiner can normally be reached on 8:00 a. m. EST. to 4:30 p.m. EST.If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Deborah Clark can be reached on (703)-305-4051. The fax phone numbers for the organization where this application or proceeding is assigned are (703)-308-

4242 for regular communications. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703)-308-0196.

Beena Puri, Ph. D.
Patent Examiner
Art Unit 1633
January 14, 2002

DAVID GUZO
PRIMARY EXAMINER